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THE SIGNIFICANCE OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN YOUNG ADULTS

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Submitted for publication, June 23, 1943

I. INTRODUCTION

In the world today a far greater number of young adults are undergoing rigorous cardiovascular scrutiny than ever before. Millions in this country and in others are being examined for the Army, the Navy, the Air Corps and the other armed services, as well as for defense industries, which are also maintaining very high standards, where cardiovascular disease is concerned. Many are reexamined when they are hospitalized because of infection, injury or other cause. With such large groups of individuals involved, the instances in which the possibility of organic heart disease arise are numerous. Clinical data of questionable significance include: (1) a history of rheumatic fever, (2) a history of precordial pain or palpitation, (3) a rapid heart rate, (4) borderline elevation of blood pressure, (5) certain auscultatory abnormalities, such as a systolic murmur or a loud third heart sound. How much help may we expect from the electrocardiograph in the solution of such problems?

Since the first World War the electrocardiograph has come into general clinical use. First used chiefly in the field of cardiac arrhythmias, it has been extended more and more toward the less secure realm of detecting degenerative changes in the myocardium, and more recently still, electrocardiographic patterns (1, 2) have been described which are considered specific for certain anatomical abnormalities of the heart. Most of the electrocardiographic evidence has been obtained from sick patients, many of them in hospitals, and most of them over 30 years old, except when younger patients were suffering from some special condition such as rheumatic fever. Electrocardiographic patterns have only been compared with anatomic abnormalities in patients who have *died* shortly after the electrocardiogram was taken,

usually from heart disease. Can the same interpretation be placed on electrocardiographic abnormalities that are found on routine examination of subjects who are young and healthy?

II. NORMAL STANDARDS

Only in late years has there begun to be adequate recognition of the wide variations of the normal human electrocardiogram. Sir Thomas Lewis and Gilder (3) published the criteria of the normal electrocardiogram in 1912 based on a study of 53 young male adults. Almost the only extensive study that has appeared since that time up to 1940, is that of Ferguson and O'Connell (4), who in 1926 reported a series of electrocardiograms made on 1812 midshipmen at Annapolis without heart symptoms and considered free from heart disease (except in three instances). Of the 1812 tracings examined 52 per cent were considered by them to be perfectly normal; a large additional number showed changes such as inversion of the T wave in the third lead to which no importance was attached. There were, however, 119 instances of right and 115 of left axis deviation, 27 instances of extrasystoles, 26 of P-R interval greater than 0.20 second, 8 instances of T II being inverted, diphasic or iso-electric, 2 instances of prolongation of the QRS complex and 2 instances of sino-auricular block. The authors were unable to correlate the electrocardiographic abnormalities with any positive points in the history or physical examination, nor in the 48 instances of axis deviation in which teleoroentgenograms were taken could any correlation be found between the extent of axis deviation and the size of the heart. They believed that the discrepancy existing between the electrocardiographic and X-ray findings was due to a rotation of the heart on its vertical axis. In a number of instances, axis deviation or abnormal T II waves were no longer present when a second electrocardiogram was taken. They concluded that electrocardiograms proved of no value in assessing the heart's condition in the 1809 men who were believed to have normal hearts; certain anomalies were found which could not be demonstrated as pathological.

A similar study (5) published in 1942 was carried out on 2000 members of the Royal Canadian Airforce Aircrew who had passed their standard medical examination for "Fitness for Flying." The records thus obtained were divided into 5 categories:

	Records	%
I. "Textbook Normal"	27	1.35
II. Normal type more frequently seen	358	17.9
III. Normal variations	1,307	65.3
IV. Doubtful abnormal	299	14.9
V. Definitely abnormal	9	0.45

Category III included P negative or absent, Q, R or S splintered or notched, S-T elevated or depressed, auricular or ventricular extrasystoles, R less than 5 mm. in one or two leads and T negative or diphasic in Lead III. By far the largest number fell into this category. Considered "doubtful abnormal" were low voltage of R wave in all leads, left or right axis deviation, prolonged P-R, prolonged QRS. As "definitely abnormal" were cited T wave negative in Lead I, Lead II or both and bundle branch block.

Wood, Wolferth and Miller (6) surveyed a number of smaller groups of college students, whom they consider correspond roughly in age to army recruits. They, too, noted electrocardiographic abnormalities similar to those already listed. They made every effort to correlate single electrocardiographic abnormalities such as low T waves with clinical abnormalities such as a history of scarlet fever or diphtheria, systolic murmurs, or reduplicated heart sounds. However, after careful consideration of all the groups, it was found that the subjects with normal electrocardiograms had as high an incidence of minor clinical abnormalities as any group whose electrocardiogram showed one or another type of deviation from strict normality. Moreover, no group with one or more of the aforementioned clinical abnormalities showed a higher incidence of minor electrocardiographic abnormalities than did the students with no clinical abnormality. They conclude that "in persons under 30, electrocardiographic study does not demonstrate abnormalities of importance from the military standpoint which are not discoverable on physical examination. Moreover, in the study of young persons in whom heart disease is present or is suspected to be present electrocardiography rarely adds further significant information. Finally, it may confuse the issue by discovering minor abnormalities in persons who have no cardiac lesion of military significance." This statement, from physicians who are among the chief exponents of electrocardiography in this country, deserves a great deal of thoughtful attention.

The interpretation of inverted T I or T II when found in electrocardiograms taken in civilian hospitals varies from a bold "indicates myocardial disease" or even "coronary disease," to a more cautious "suggests myocardial damage" depending on the degree of conservatism of the interpreter. Yet when we realize that there may well be 20,000 individuals in our army today who would exhibit this electrocardiographic abnormality without any clinical cardiac abnormalities, we should certainly hesitate before labelling them as having heart disease, or even as being persons especially liable to develop degenerative heart disease in the future.

III. EXPERIMENTAL WORK

Clues as to the nature of at least some of these abnormalities may have been furnished by recent physiological studies. Nahum and Hoff have carried out fundamental experiments to explain the genesis of the normal electrocardiogram, publishing their results in a series of papers appearing in the American Journal of Physiology in 1940 (7, 8, 9), 1941 (10, 11, 12) and 1942 (13). In the course of their experiments they have reproduced most of the abnormalities under discussion in reversible form. For years it has been postulated that the electrocardiogram is the summation of electrical events from the two ventricles, each ventricle acting as a unit and giving rise to its own electrogram. These are designated as dextro- and levocardiograms, and are believed to be of opposite polarity, and slightly out of phase with one another. By blocking one or the other bundle branch, Sir Thomas Lewis was able to delay one electrogram enough to expose the initial portion of the other, and to show that in the initial phases, at least, the normal electrocardiogram was the algebraic summation of the dextro- and levocardiograms. Until the work of Nahum and Hoff, however, efforts to obtain complete electrograms of the left and right ventricles had been unsuccessful.

Their method is based upon the following two observations (14): (a) The electrocardiogram is determined by activity at the surface of the heart. (b) Potassium chloride in fifth molar solutions extinguishes electrical activity at the point of its application to the surface of the heart.

By covering large portions of the surface of a single ventricle with filter paper soaked in KCl solution it was thus possible to expose the

electrogram of the untreated ventricle. Dogs, cats and monkeys were the experimental animals used.

When a large portion of the surface of a single ventricle was treated with KCl solution, an electrocardiogram (taken by the standard limb leads) was obtained which resembled closely the monophasic records that have been derived directly from the surface of the heart. A dextrocardiogram and a levocardiogram could be obtained successively by first applying the KCl solution to the left ventricle, and, after removing the filter paper and allowing for a period of recovery, then applying it to the right ventricle. Whether the T wave resulting from the algebraic summation of the terminal portions of these electrograms was upright or inverted depended upon the relative duration of the levocardiogram and the dextrocardiogram.

Nahum and Hoff drew certain conclusions about the genesis of the electrocardiogram from these experiments. They considered that the monophasic character of the electrogram of each ventricle indicates that each ventricle fires as a unit with practically simultaneous discharge of all its fibers. The right ventricle is activated first, and contributes Q and the upstroke of R. At this time the left ventricle is activated, and the potential is equalized, forming the downstroke of R and S. During the ensuing S-T interval both ventricles are active, but their opposite electrical potentials neutralize each other at the distant leads. If the dextrocardiogram persists after the levocardiogram is ended, the T wave is upright. If cessation of activity in the right ventricle occurs before that of the left, a downward T wave results.

These workers then continued to explore the significance of various electrocardiographic abnormalities. Instead of extinguishing the electrical activity over the surface of an entire ventricle, they used small pledgets soaked in KCl solution so that electrical activity was abolished over small localized areas. They found that elevation of the R-T segment in any lead denotes damage to the surface of the left ventricle, while depression of the S-T segment in any lead indicated damage to the surface of the right ventricle. When electrical activity is extinguished in a portion of the heart by KCl, an imbalance is created between the dextro- and levocardiograms, and the undamaged ventricle preponderates, producing either an elevation or a depression of the RST segment.

When a pledget was placed over a single ventricle, the RST interval was deflected in the same direction in all three leads. However, when a KCl-soaked pledget was placed in such a way that it bridged the septum and covered contiguous portions of *both* ventricles, mixed effects were obtained. Placed anteriorly, it produced in Lead I an upward displacement of the RST segment, and a downward one in Lead III. Combined effects from the apex and whole posterior septal region showed the opposite picture; the RST segment in Lead I was invariably deflected downward, while in Lead III it was upward. The electrocardiographic changes produced by pledgets covering part of both ventricles compare closely to those ascribed to acute infarction.

Pursuing their study of factors determining the direction of the T wave still further, the same investigators altered the duration of the dextrocardiogram or levocardiogram by applying heat or cold separately to each ventricle. Just as heating or cooling the animal as a whole shortens or lengthens the ventricular complex of the standard electrocardiogram, so by localized heat were they able to shorten and by localized cold to lengthen the electrogram from a single ventricle. They found that cooling the surface of the left ventricle invariably produced a sharply inverted T wave with prolongation of the duration of the Q-T interval, while cooling the right ventricle produced an upright T wave which was also prolonged. Heating the surface of the left ventricle produced an acutely upright T wave of normal duration, while heating the surface of the right ventricle produced a sharply inverted T wave of normal duration.

Similar studies have been conducted by them on the other portions of the ventricular complex. Perhaps the most significant of these for our purpose is a recent paper demonstrating that the Q wave can be exaggerated or suppressed by the proper application of heat or cold to the two ventricles.

From the clinical standpoint, several interesting concepts arise out of this work: first, that abnormalities of the electrocardiogram which have too frequently been interpreted as definite indications of "myocardial damage" such as inversion of T waves, or exaggeration of Q waves may be produced experimentally by such simple stimuli as local applications of KCl or heat or cold to the epicardium alone. Second, that these changes may be reversible, and quite rapidly so, so that the electrocar-

diogram returns to normal within a matter of minutes after the removal of the stimulus. Third, that changes very similar to those seen in myocardial infarction arise when abnormal electrical activity is induced at the surface of the heart, and that these, too, are reversible. The electrocardiographic changes thus produced may also simulate those encountered clinically in acute pericarditis.

IV. CLINICAL OBSERVATIONS

In the last few years several clinical studies have pointed out special circumstances under which the QRS-T segment of the human electrocardiogram becomes temporarily abnormal. Sigler (15) in 1938 compared the electrocardiograms of 100 subjects when tracings were taken both in the recumbent and standing positions. Upon standing, normal T waves became flattened or even inverted, and definite changes occurred in the appearance of the QRS complex in many cases. Ylvisaker and Kirkland (16) in 1940, likewise found that marked changes in T wave configuration were produced by altering the position of the body. Their interest in the problem was awakened by the discovery of abnormal T wave changes, notably inversion of T II, in a group of apparently healthy young subjects. The original tracings had been taken with the subjects in the sitting position. In every instance, when the tracings were repeated with the patient recumbent, T II became normally upright. Those who showed these changes were usually young and of slender build; many were highly nervous and clearly showed the characteristic signs of vasomotor imbalance. In no instance was there sufficient change in blood pressure to warrant a diagnosis of orthostatic hypotension. As a consequence, they recommended that all electrocardiograms should be made with the subject in the recumbent position.

White and Graybiel (17) have also noted inversion of the T wave in lead II in occasional normal young persons, particularly those of asthenic habitus and subject to neurocirculatory asthenia, upon assuming the erect posture. They have recently pointed out that the lowering, flattening, notching or inversion of T II thus produced may be partially or completely restored to normal if the subject hold his breath in complete expiration, thereby elevating the diaphragm. They therefore conclude that the position of the heart itself is the most important factor in producing this T wave inversion produced by the erect posture.

Mainzer and Krause, 1940 (18), have described the influence of fear upon the electrocardiogram. Tracings were taken on 53 patients immediately before the induction of general anesthesia, when the patients were apprehensive over the impending operation, but otherwise at rest and not under the influence of any drugs. These records were compared with tracings taken the day before and the day after operation, and also with tracings taken during anesthesia. Electrocardiographic changes which the authors attribute to fear alone were present in nearly half of the cases, many in patients under 30. These changes consisted chiefly in S-T depression and lowering or inversion of the T waves similar to that appearing in coronary insufficiency and ascribed by the authors to neurogenic influences reducing the coronary flow. In 5 cases out of the 24 showing preanesthesia changes the tracing returned to normal as soon as anesthesia was induced; in 17 the deformation had disappeared completely by the following day, but in the remaining 3 it had not.

May (19), in studying the effects of anoxemia upon normal subjects, found that during oxygen deficiency the T waves were uniformly and progressively flattened in all three leads, and the S-T segments were occasionally depressed. He reported that the degree of T wave flattening was very high in young subjects, and diminished greatly with advancing age. There was a striking correlation between the amount of bodily activity and the degree of electrocardiographic change. Complete eradication of the T wave during anoxemia was seen only in very active or athletic young people. This study is of particular interest because it suggests the likelihood that other influences, more physiological than oxygen deficiency, may likewise alter the electrocardiogram of normal active young persons to a greater degree than the electrocardiograms of older individuals.

Another electrocardiographic abnormality to which young people are liable is the syndrome first described by Wolff, Parkinson and White (20) in 1930 as "Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia." This syndrome, though uncommon, is now well known, and it is recognized that the bizarre electrocardiograms do not necessarily represent cardiac damage. One group of investigators has suggested that the electrocardiographic changes represent true bundle branch block, while a larger group believe that it is only an apparent bundle branch block due

to ventricular asynchronism, with premature stimulation and contraction of one ventricle. The premature stimulation of one ventricle has been considered to be due to an abnormal conducting system between the auricle and ventricle, such as the bundle described by Kent in 1892.

Butterworth and Poindexter (21) have been the first to experimentally reproduce this syndrome, in which the auriculoventricular conduction time is shortened as the intraventricular conduction time is prolonged, so that the total time necessary for the impulse to pass from the sino-auricular node to the ventricular muscle is unchanged. Using cats and dogs, they tried to form new conduction pathways from auricle to ventricle by connecting the auricular appendage to the corresponding ventricle by platinum wire, by needles, by wick bridges soaked in physiological salt solution, and by suturing. All these attempts failed to produce any electrocardiographic changes. However, when the current generated by the auricular muscle was picked up by electrodes on the surface of the auricle, amplified several thousand times and used to stimulate one ventricle by similar electrodes placed on the ventricular epicardium they were able to short circuit the normal conduction system of cats' and dogs' hearts. One ventricle was stimulated to contract earlier than it would otherwise have done. The auricular components of the standard electrocardiogram remained perfectly constant, but by turning the amplifier on and off, abnormal complexes of the short P-R wide QRS type could be produced at will. When the flow of current through the abnormal conduction pathway was reversed, tachycardia was produced.

V. CONCLUSION

In summary, then, there are a number of physiological mechanisms which may alter the electrocardiogram, sometimes to an abnormal degree; I have only mentioned some of the outstanding ones. In the age groups in which degenerative disease of the myocardium is rare, there is greater likelihood that a given electrocardigraphic abnormality is a physiological variant than evidence of a pathological lesion. Until the limits of normal variation in the human electrocardiogram have been much more thoroughly explored, the diagnosis of heart disease in young persons should seldom be based on electrocardiographic findings alone, in the absence of clinical manifestations.

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CONGENITAL CHICKENPOX WITH DISSEMINATED VISCERAL LESIONS

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This case of congenital chickenpox, resulting in death, is unique, as a search of the literature fails to reveal a single autopsy of this condition. Shuman (1) reported a case of placental chickenpox transmission, but the infant's chickenpox was mild and resulted in recovery. Shuman found 6 similar cases in the literature. Recovery occurred in the cases of Cosgrove and Samuel, Pridham, Senator, Henderson, and Mitchell and Fletcher. Baron's infant developed chickenpox on its eighth day of life and died at eleven days, but there was no autopsy. Two more cases of congenital chickenpox have been found (Hubbard (2) and Campbell (3)), bringing to nine the total number of previously reported cases of congenital chickenpox. These last two reports, like the earlier ones, are only clinical descriptions, as both infants recovered.

The present case is that of a female colored infant dying at eleven days, showing not only a rash, typical of chickenpox, but widely disseminated visceral lesions. The association of visceral lesions with the rash is not unknown, though it is quite rare. Johnson (4) reported a case of a seven months old boy and illustrated beautifully the necroses and associated inclusion bodies found in the skin, oesophagus, pancreas, liver, renal pelves, ureters, bladder and adrenals. A pair of three weeks old twins, dying with varicella, were described by Schleussing (5); they also showed visceral lesions consisting of focal necroses in the liver, adrenals and spleen, similar to those in Johnson's case, although no inclusion bodies were described in them. No other pathological report of disseminated chickenpox can be found.

CASE REPORT

The patient's mother, a 19 year old colored woman, broke out with a rash, typical of chickenpox, when seven months pregnant. The chickenpox was mild but resulted in the birth of a premature female infant five days after the appearance of the rash. Delivery was per-

formed at home and there was no microscopic examination of the placenta.

At birth the patient weighed 4 lbs. On the fifth day of life the infant developed a suppurative exudate in both eyes; two days later a papulovesicular rash was noted and treated by rubbing with olive oil.

The patient was admitted to the hospital when nine days old, two days after the appearance of the rash. Temperature was 34.6°C. Examination showed a papulovesicular eruption involving the scalp and the whole body except the palms and soles. No lesions were noted in the mouth, but several were seen in the vagina. There was a suppurative exudate in both eyes. The spleen was palpated. Otherwise no abnormalities were seen.

The rash appeared quite uniform and consisted mostly of small vesicles, although rare pustules, crusts and confluent lesions were present. The absence of crops of lesions, and the absence of mouth lesions, suggested that something other than chickenpox might be responsible for the condition.

Cultures of conjunctiva and vesicles showed secondary infection with hemolytic staphylococcus albus. On the eleventh day of life, respiratory distress occurred and was followed by death. Post-mortem blood cultures, taken within 20 minutes of death by the clinician were positive for B. aerogenes and B. hemolytic streptococcus. These were thought to represent a terminal blood stream invasion.

The clinical diagnosis of chickenpox was made certain by two contact cases. The student nurse who cared for the patient on the night of admission, and who had no other contact with any case of chickenpox, developed a typical chickenpox rash fourteen days later. This proved to be a mild case and ran a typical course.

The second contact case was an infant removed from the premature room one day after the death of the patient. Fourteen days later she developed a typical chickenpox exanthema. As there was no direct contact, this infection was probably carried by nurses or doctors.

Autopsy (No. 18350) was performed 17½ hours after death by Dr. Philip Wagley. The body weighed 1.7 kilograms and measured 43 cm. in length. Nutrition was poor. A vesicular rash was present over the entire face and trunk. It was less extensive on the arms and legs, and no vesicles were seen on the extensor surfaces of the arms or on

the scalp. The vesicles were small, not over 5 mm. in diameter, and all appeared of approximately the same age. A few crusted lesions were also noted.

The eyelids were adherent and showed crusting at the borders; the conjunctivae and sclerae were reddened and there were areas of shallow erosions in the conjunctivae.

The serous cavities were normal in appearance. The heart weighed only 11.5 grams and was entirely normal. The thymus weighed 4 grams.

The lungs showed considerable edema, and what seemed to be small patches of consolidation were noted in all lobes.

The liver weighed 70 grams. Scattered through its cut surface minute white opaque foci were noted. Some were pin-point in size, whereas others measured 2 mm. in diameter.

The spleen, though weighing only 10 grams, seemed swollen and its capsule was tense. Minute white opacities, similar to those seen in the liver, were scattered through its pulp.

The intestinal tract showed numerous lesions, similar wherever seen. They were found in the mucosa of the stomach, jejunum, ileum, colon and rectum, and consisted of shallow erosions with yellow centers, surrounded by an injected border.

The kidneys showed numerous little hemorrhages on their surfaces as well as on the cut sections. These varied in size, but some of them were obviously too large to represent hemorrhages in Bowman's capsules or tubules.

No gross lesions were seen in the pancreas, adrenals, bladder, genitalia, neck organs, arteries, lymph nodes, muscles, bones or central nervous system.

Cultures of the heart's blood were sterile.

On microscopic examination, not only were lesions found in the skin and viscera in which gross changes had been observed, but disseminated lesions were found almost everywhere in the body. The routine sections were stained with hematoxylin and eosin, but phloxine and hematoxylin stains were used to intensify the brilliant intranuclear inclusions.

The *skin* showed lesions varying in age from fresh papules of hyperplastic epithelium, to encrusted vesicles. The earliest lesions con-

sisted of small areas of epithelial hyperplasia, in which almost every cell seemed swollen. Even under low power it was noted that the cells seemed enlarged, mainly because their nuclei were also swollen and altered. With high power magnification the intranuclear inclusion bodies could be seen. They consisted of a hyaline pink mass surrounded by a clear halo, and all the nuclear chromatin seemed concentrated in a peripheral line.

An older skin lesion showed beginning vesiculation, with many of the altered cells containing a clear space in their cytoplasm about the nucleus. In the central area these cells became necrotic, and formed vesicles, surrounded by epithelial cells, still living but containing the intranuclear inclusion bodies. The oldest lesions consisted of several such lesions becoming confluent; then the vesicle was covered by a necrotic layer of unrecognizable material in which occasional remnants of cellular debris could be seen.

Many of the skin lesions were sectioned and in only one was there any reaction in the dermis. In this one section there was a fairly diffuse infiltration with polymorphonuclear neutrophiles, the lesions just described being found in the overlying epidermis. No inclusion bodies were found in the dermis except in epithelial cells of affected hair follicles.

In the *esophagus* papular areas of epithelial hyperplasia, similar to skin papules, were found. They contained similar swollen cells and altered nuclei with intranuclear inclusions. None of these lesions showed vesiculation or extensive necrosis. In the underlying submucosa the vessels were dilated and mononuclear wandering cells were seen in small foci; but no inclusion bodies could be found except in the epithelial lesions.

In the *stomach* and *intestines*, sections of the gross lesions showed superficial necrosis in the mucosa; in some areas necrotic tissue was lost, forming shallow ulcers extending into the submucosa and occasionally causing necrosis of small vessels. Epithelial cells adjacent to such areas of necrosis contained the familiar pink intranuclear inclusion bodies and peripheral margination of nuclear chromatin. There was a meager infiltration of mononuclear cells and polymorphonuclear eosinophiles in the underlying submucosa.

The *lungs* showed most interesting lesions. The areas interpreted

grossly as areas of consolidation, were revealed microscopically as zones of necrosis. Some of these were quite minute, but others involved groups of alveoli, with their dependent bronchi and vessels. Occasional inclusions could be seen at the margins of these necroses, in alveolar epithelial cells. But where the necrosis involved only a portion of a bronchiolar wall, the adjacent bronchial epithelium showed most beautiful intranuclear inclusions in all of the remaining and still living cells. No inclusions were found in involved blood vessels, or cells other than epithelial. There were patches of pulmonary edema, but no areas of inflammatory cell reaction were seen in the alveoli or bronchi. Bacterial stains revealed an occasional colony of Gram positive cocci in the coagulated edema fluid in a few alveoli and bronchi, but no organisms were stained in relation to the focal necroses.

The *liver* showed myriads of focal areas of necrosis. They occurred in no relation to the liver lobule. When contiguous to a portal area, the involved bile duct epithelium always contained beautiful intranuclear inclusions. Elsewhere the inclusions were not numerous, but occasional ones were seen in the liver cords adjacent to an area of necrosis. Numerous islands of extramedullary blood formation were seen in the sinusoids.

The *pancreas* also showed small focal areas of necrosis and adjacent acini showed intranuclear inclusions in every cell. There was no concomitant inflammatory reaction.

The *adrenals* showed similar small areas of cortical necrosis. Again the adjacent cords of glandular epithelium showed the typical inclusions, although they were not so numerous as in the pancreas.

The *kidneys* showed fairly large areas of cortical necrosis. As the vessel walls were involved in the process, there was always an associated interstitial haemorrhage. The epithelium lining the adjacent tubules contained the familiar pink intranuclear inclusion bodies.

The *thymus* showed rather large areas of necrosis, involving particularly the medullary tissue rather than the lymph cords. The outlines of completely necrotic Hassall bodies could be recognized in the necrotic zones, but when still intact Hassall bodies were adjacent to these areas, their epithelial cells contained beautiful inclusions.

In the *spleen* there were scattered small focal necroses; and in some of these areas necrotic thrombosed arterioles were noted. Larger,

infarct-like, necroses were also present, evidently the result of the vascular occlusions. No inclusion bodies were seen in relation to the latter, but a most careful examination resulted in finding a few questionable inclusions in the periphery of the smaller necroses. The exact nature of the cells with inclusions was not altogether clear. They were presumed to be sinus endothelium.

In the *bone-marrow* of the vertebra and ribs there were also focal necroses. No inclusion bodies could be found in these tissues.

No abnormalities were found in the other tissues. It should be noted, especially, that no chickenpox necroses or inclusions were seen in the available sections of mesenteric and mediastinal lymph nodes, thyroid, heart, striated muscle, aorta, bladder, ureter, kidney pelves, uterus, cervix or vagina, or pharynx. Clinically, however, several lesions were noted in the vagina. Numerous sections of the brain were normal. The eyes were not examined microscopically.

Anatomical Diagnosis: Congenital Chickenpox. Disseminated vesicular rash, conjunctivitis, scleritis, and blepharitis. Necroses with intranuclear inclusion bodies in skin, oesophagus, stomach, intestines, lungs, liver, pancreas, adrenals, kidneys (with petechial haemorrhages), thymus and spleen. Necroses without inclusion bodies in marrow of ribs and vertebra. Pulmonary edema. Prematurity.

DISCUSSION

This is undoubtedly a case of congenital chickenpox and the intrauterine transmission of the virus occurred at least five days before birth. With the appearance of the conjunctivitis 5 days after delivery, the incubation period was a minimum of ten days. But as it is impossible to determine exactly when placental transmission occurred, it may have been considerably longer. Clinically, before the contact cases made the diagnosis certain, the apparent uniformity of the lesions raised the possibility that they might be caused by something other than chickenpox. However, histologically the lesions varied in age and indicated that they did, in fact, occur in crops. Furthermore, the mother's chickenpox was identified by at least three physicians; and the contact cases removed all doubt as to the absolute diagnosis of chickenpox.

The lesions were widely disseminated throughout the body; yet, if

the intranuclear inclusions may be taken as an indication of the actual presence of the virus, there is a striking demonstration of its affinity for epithelial structures. The inclusions were seen in the squamous epithelium of the skin and esophagus; in the columnar epithelium of stomach, intestines, bronchioles and bile ducts; in the glandular epithelium of liver, pancreas and adrenals; in the epithelium lining renal tubules and pulmonary alveoli; and in the epithelium of Hassall's bodies in the thymus. The only location where the inclusions are not specifically epidermotropic is the spleen, and here they were imperfect in structure and the cells in which they are seen could not be identified with certainty. It is true that focal necroses occurred not only in conjunction with the inclusions but more widely in the spleen, and also in the bone-marrow in their absence. It was not possible to determine which cells in the necrotic areas were first involved, but the effect of the spreading necroses was evident, with hemorrhages from necrotic vessels and infarct-like splenic infarctions from thrombosed arterioles. Vascular necroses were, in fact, prominent in many of the larger areas of disseminated necroses; but, no inclusion bodies were found in the endothelial or other cells in the affected vessel walls or lumina. Their absence from vascular endothelium is added evidence of the epidermotropism displayed by this virus as there had obviously been hematogenous spread of the virus and yet injury to the vessel wall appeared to be only a sequel to the intraepithelial growth of the virus. Two exceptions to this observation must be noted. Necroses were found in the spleen and bone-marrow without the presence of epithelial cell inclusions indicating the growth of the virus

No studies were made on the nature of the virus clinically, or after death. That the lesions are due to the virus of chickenpox seems certain. Intranuclear inclusion bodies in the epithelium of the skin have been repeatedly described in this condition (Tyzzer (6)); they have been classified by Cowdry (7) as Type A inclusions, and these same inclusions in association with the disseminated necroses give evidence that the virus is similarly disseminated. No bacteria were stained in any of the lesions. There is almost no inflammatory cell reaction and certainly none at all in conjunction with the necroses. It is safe to conclude that the necroses, even in the absence of the inclusion bodies, were all due to the widespread distribution of the chickenpox virus rather than to any superimposed secondary infection.

It is interesting that in spite of the blood-stream distribution of the virus there was found no encephalitis, nor any lesion in the central nervous system.

The distribution of the visceral lesions in this congenital case of chickenpox is similar to, though somewhat more extensive than in the three contact cases of visceral chickenpox in the literature. Schleussing's (7) twins, as well as Johnson's boy (4) showed necroses in the liver and adrenals; the former also contained necroses in the spleen. Johnson's case showed additional lesions in the epithelium of the skin, esophagus, pancreas, bladder, ureters and renal pelves, as well as inclusion bodies in vascular and lymphatic endothelium and histiocytes. In this case all of these structures were involved with the exception of the transitional urinary tract epithelium, and endothelial structures. But additional lesions were found in the epithelium of the stomach, intestines, renal tubules, bronchioles and pulmonary alveoli, thymus and bone-marrow.

SUMMARY

A case of congenital chickenpox is described in a premature infant dying at eleven days. Disseminated necroses with associated epithelial intranuclear inclusion bodies were found in the skin, esophagus, stomach, intestines, pancreas, lungs, bronchioles, kidneys, liver, adrenals, thymus, and possibly spleen. Necroses without inclusion bodies were found in the bone-marrow.

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EXPLANATION OF PLATES

(Photographs by Miss Dorothy Schmitt)

FIG. 1. Low power photograph of small focus of necrosis in lung, which extends into wall of bronchiole. (H. and E.).

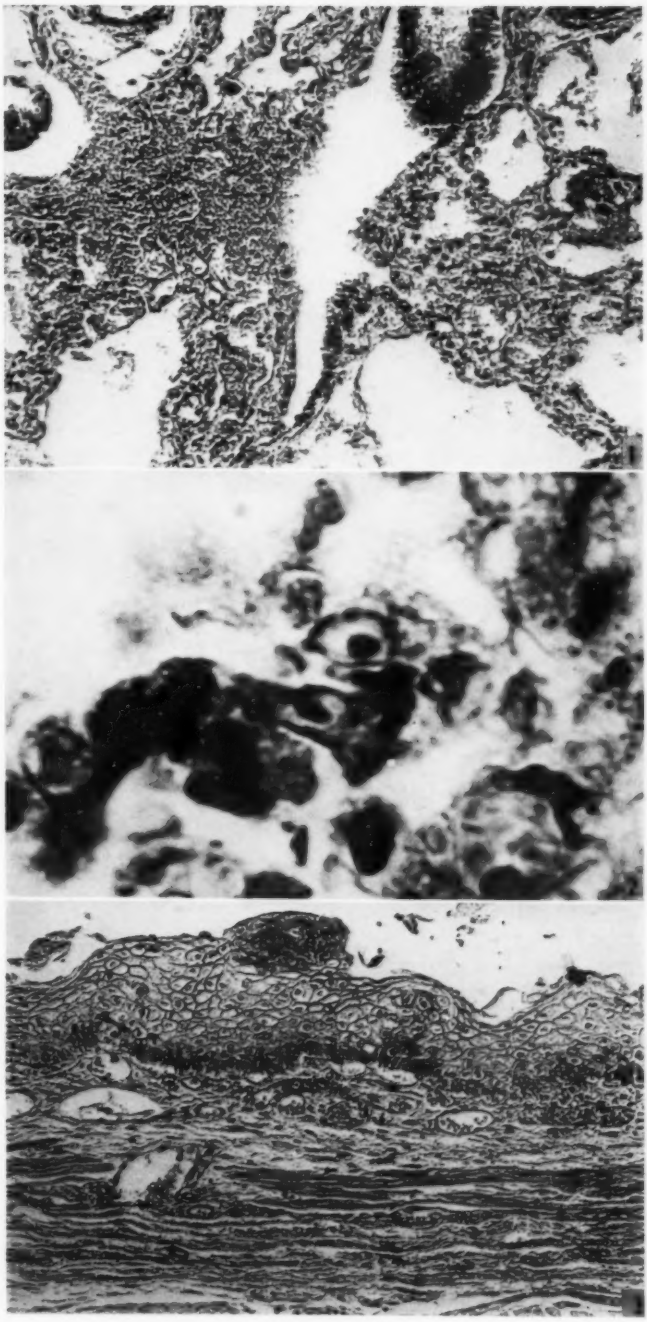
FIG. 2. High power magnification of bronchial mucosa showing three distinct intranuclear inclusions (Phloxine and hematoxylin). The inclusions are eosinophilic and surrounded by a clear space in the nucleus. The nuclear chromatin is condensed at the periphery of the nucleus.

FIG. 3. Low power magnification of esophagus (H. and E.). A small area of necrotic epithelium covers an area of slightly hyperplastic epithelial cells. No inclusions can be seen in this magnification, yet under high power they may be seen in every hyperplastic epithelial cell in this region.

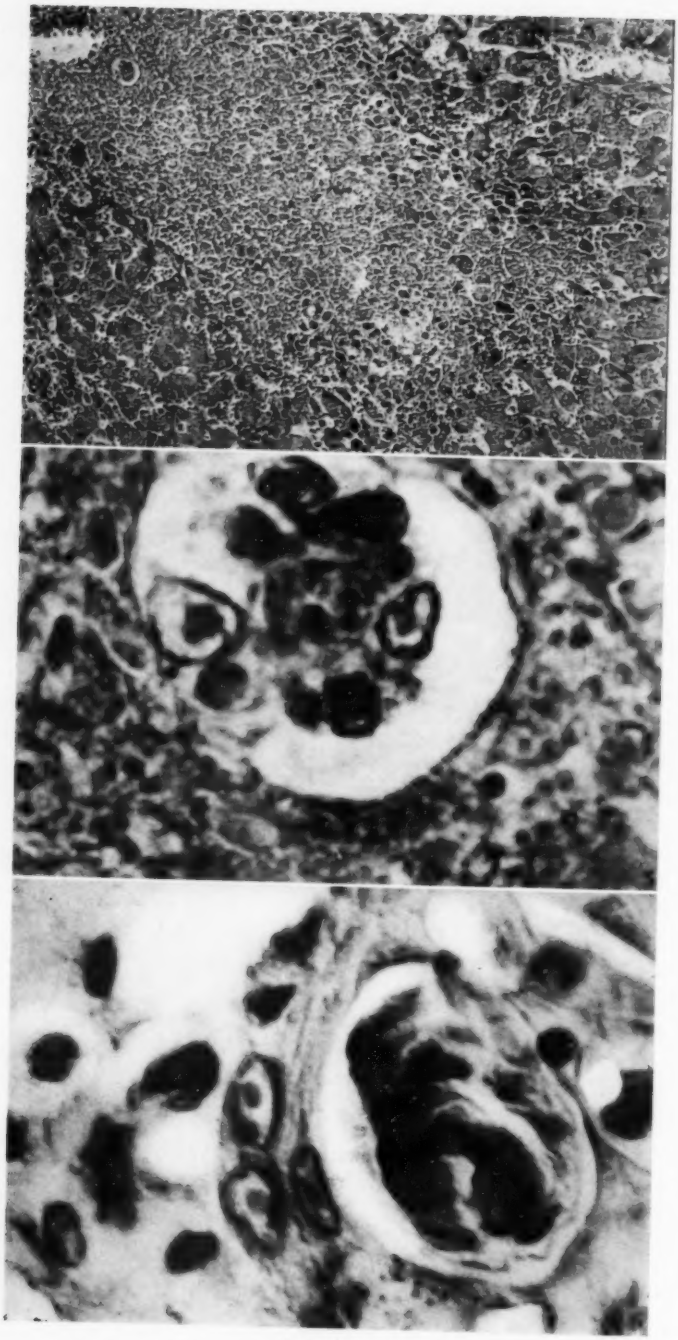
FIG. 4. Liver, low magnification, showing an area of necrosis involving hepatic cords and a portal space (H. and E.). A small bile duct may be seen near the left upper corner.

FIG. 5. Liver; high power of bile duct seen in Fig. 4 (Phloxine and hematoxylin). The intranuclear inclusions are seen in four cells.

FIG. 6. Thymus. High power magnification of a Hassall body, showing three intranuclear inclusion bodies in the peripheral epithelial cells of this structure (Phloxine and hematoxylin).



FIGS. 1–3



FIGS. 4–6
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OBSERVATIONS ON A HISTIDINE DEFICIENT DIET IN MAN[1]

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The role of histidine as a dietary essential has been studied extensively in the rat. The conclusion seems well established that in this animal histidine is a growth essential, as was first shown by Cox and Rose (1). It is by no means as clear, however, that histidine is needed for the maintenance of the adult rat. Although the studies of Wolf and Corley (2) pointed to that conclusion, the observations of Burroughs, Burroughs and Mitchell (3) indicated that the rat could be maintained in nitrogen equilibrium in the absence of this amino acid.

Data on the essentiality of histidine for man have not been hitherto reported, nor is it possible to assume that the situation is similar to the rat, since a number of differences in amino acid requirements have been encountered even in closely related animal species. In the course of studies designed to throw light on human amino acid requirements, some of which have already been reported (4) we undertook to study the human requirement for histidine. The present report presents data from three experiments on a histidine deficient diet which were carried out in May and June, 1943.

As in our previous studies three normal adult males were submitted to an experimental diet consisting of fats, starches and certain fruits and vegetables of low protein content which provided approximately 10 per cent of the daily nitrogen intake.[2] The remaining 90 per cent

[1] Aided by grants from the Rockefeller Foundation, Merck and Company, E. R. Squibb and Sons and The Nutrition Foundation. Partial support was also derived from the Office of Scientific Research and Development under contract OEM-cmr-362.

[2] These menus consisted of fruit juices, fresh and canned fruits and vegetables. A typical menu for a 70 kg. male follows: *Breakfast:* 200 cc. orange juice, 100 g. applesauce, 1 piece starch cake with honey, tea or coffee; *Lunch:* 200 cc. tomato juice, 50 g. buttered string beans, 100 g. scalloped potatoes, celery hearts and cucumber salad, baked apples with hard sauce, iced tea or coffee; *Dinner:* 200 cc.

was supplied as a histidine-deficient casein digest prepared by a slight modification of the procedure of Cox and Berg (5). Analysis of the final hydrolysate showed that histidine had been almost completely removed, whereas the arginine content remained unaffected (histidine content 0.07%; arginine content 3.1%). This product was supplemented with 1.5% *l*-tryptophane and 1.0% *l*-cystine for use as the histidine deficient digest. In the present experiments the caloric intake was maintained between 38 and 43 calories per kilo per day, and the nitrogen intake at 0.1 gm. per kilo per day.

The subjects pursued a sedentary life throughout the experimental period. In order to expedite the attainment of N-equilibrium they were given a low protein diet for 2 days before the onset of the experiment. A 6-day control period was then instituted on the histidine-deficient diet supplemented with *l* (+) histidine HCl to the extent of 1.9% of the protein moiety (equivalent to 1.5% *l* (+) histidine). This was followed by 36 days on the deficient diet after which a post-control period was carried out with step-wise supplementation with histidine; for 3 days *l* (+) histidine was added to the extent of 0.5% of the protein moiety, for another 3 days this supplement was increased to 1% and for the final 6 days a supplement of 1.5% was added.

The nitrogen balances were determined for 3 day periods from analyses of the food and excreta. The nitrogen and sulfur metabolites of the urine were followed throughout the course of the experiment, as were the blood proteins and formed elements.

Results. None of the three subjects developed clinical symptoms, nor were any definite changes noted in their blood chemistry or morphology. The subjects all lost weight during the course of the experiment (fig. 1). Somewhat to our surprise, however, the nitrogen balances remained positive throughout, and the excretion of histidine in the urine showed no reduction.

An interesting and unexpected change was, however, encountered in the course of measuring the indican output by the Sharlit adaptation (6) of the Jolles reaction. In all of the histidine deficient subjects

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tomato juice, 100 g. cauliflower with Creole sauce, 1 medium baked potato, 100 g. pineapple salad, frozen apricots, iced tea.

We wish to thank Mrs. Rida Rutherford, our dietitician, for her assistance in this work.

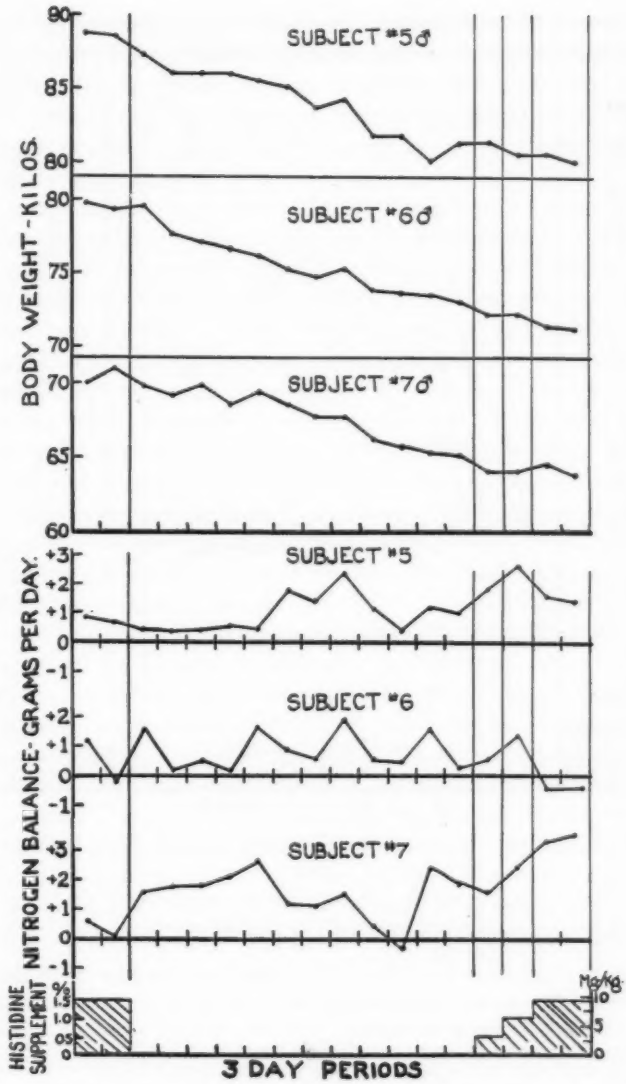

FIG. 1. THE NITROGEN BALANCE AND BODY WEIGHT CHANGES IN HUMAN SUBJECTS ON A HISTIDINE DEFICIENT DIET

an increased "indican reaction"[3] was noted (fig. 2); moreover, the color of the test differed from that normally obtained with indican, being

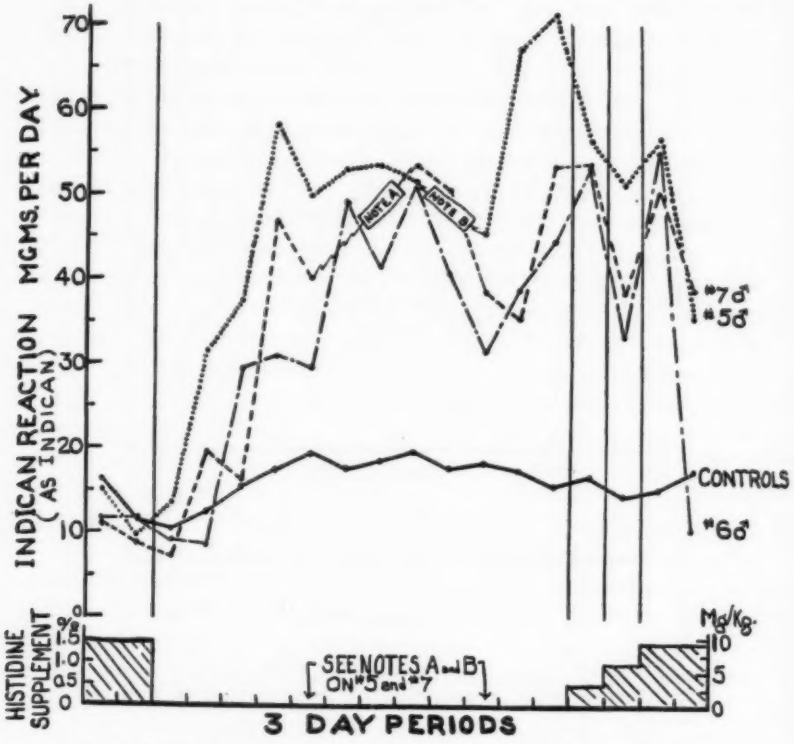

FIG. 2. VARIATION IN THE "INDICAN REACTION" ON A HISTIDINE DEFICIENT DIET

Note A. During 3 of the 10 days of the period designated by jagged line, Subject #7 received a daily supplement of *l* (+) histidine, equivalent to 1.5% of the protein hydrolysate (see fig. 3).

Note B. During 2 of the 4 days of the period designated by the jagged line, Subject #5 received a daily supplement of *l* (+) histidine, equivalent to 0.75% of the protein hydrolysate (see fig. 3).

[3] The determinations were made photometrically, using a Klett colorimeter with an S-54 filter, a filter which transmits both green and violet rays. The quantitative measurement which we have recorded as "indican reaction" therefore represents not only indican, but in addition the unknown material giving the green color.

emerald green rather than lavender in color. This behavior of the test differed markedly from that in six other subjects who were studied in parallel experiments on the same basal diet but who were on other amino acid deficiencies (2 subjects on tryptophane deficiency and 4 on a deficiency of sulfur amino acids) all of whom showed normal indican excretions with the usual lavender color.

In order to make sure that the green color reaction was specific for histidine deficiency, the experiment was interrupted in 2 of the 3 subjects for a brief period. For 3 days subject # 7 was given in place of the deficient hydrolysate an identical digest to which 1.5% *l*-histidine had been added and subject # 5 was given for 2 days a digest to which 0.5% *l*-histidine had been added, after which both subjects were continued on the deficient diet. The value for the "indican" excretion (that is excretion of indican plus that of the unknown green chromogen) as shown in fig. 3, fell promptly in the case of the subject receiving the larger supplement and coincidentally the green reaction was replaced by the usual lavender color. When the histidine deficient diet was resumed the excretion increased and the green color reappeared. In subject # 5 who received the smaller supplement a similar but less marked drop in the "indican" value occurred and the color changed from a pure green to a purplish green, these changes being reversed when the deficient diet was resumed. In the post-control period subject # 6 reverted to a normal "indican" value and usual lavender color when the 1.5% histidine supplement was given; subjects # 5 and # 7, however, showed only a partial reversion to normal during this period, the "indican" value remaining higher than normal and the color changing from green to a mixed tint of green and purple. It would appear from these findings that the excretion of a substance giving an anomalous green Jolles reaction is characteristic of histidine deficiency in man. The nature of this metabolite is now under investigation.

Comment. It is clear from our results that histidine is not essential for the maintenance of nitrogen equilibrium in the adult human. This result is in keeping with the observations of Rose *et al.* (7) a preliminary report of which appeared while our work was in progress. However, we feel some hesitation in concluding, as do the Illinois investigators, that histidine is unessential for man until further studies have clarified the picture. The loss of weight experienced by our

subjects on the histidine deficient diet remains to be explained. It is conceivable that the caloric intake of these subjects, although averaging 40 calories per kilo, was inadequate and that the loss of weight represented a loss of fat. The activity of the experimental subjects was not strictly controlled although they did not engage in active

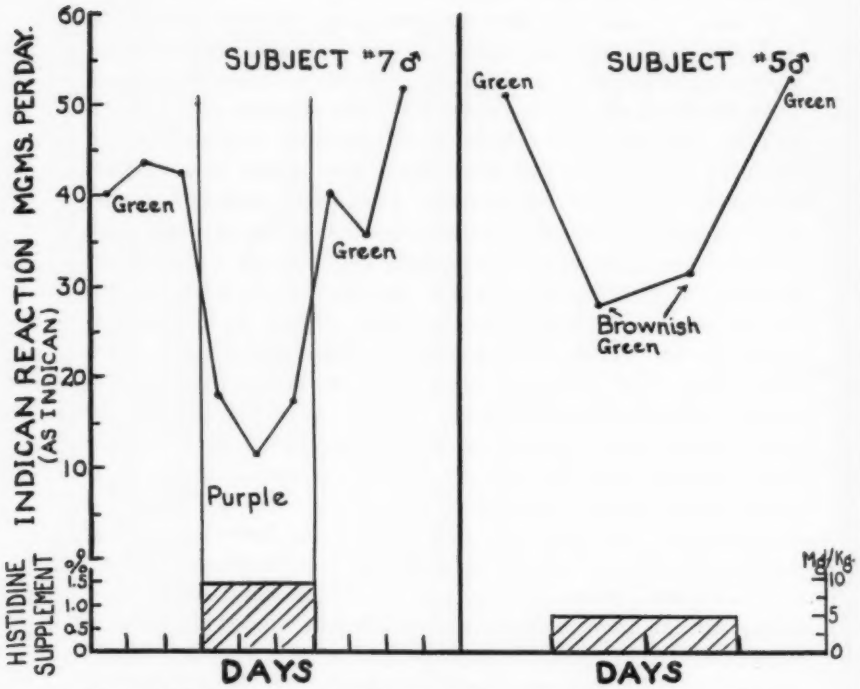

FIG. 3. THE EFFECT OF *l* (+) HISTIDINE SUPPLEMENTATION ON THE "INDICAN REACTION" OF HUMANS ON A HISTIDINE DEFICIENT DIET

exercise. If the loss of weight were due to histidine deficiency it should have been checked by the histidine supplement, but if due to inadequate calories it should have continued unchecked. Unfortunately the evidence afforded by the weight curves is equivocal on this point. Subjects #5 and #7 show evidence of arrested weight loss when the supplement was given but in subject #6 the loss of weight continued

unchecked. The abnormal metabolite in urine in the histidine deficient period does not provide evidence of the essentiality of histidine; it may represent a by-product of some synthetic reaction by which histidine is formed or may indicate a process of tissue destruction which does not result in a negative nitrogen balance. The simultaneous hypertrophy of one organ and atrophy of another may occur without affecting nitrogen balance, and numerous examples are known in which even nitrogen retention may occur at a time when atrophic changes are occuring in some vital organ. It is also possible that a histidine deficient diet may result in atrophic changes in some essential tissue which represents such a small fraction of the body that its disintegration is not detected in a nitrogen balance study. In this connection we may refer to our previously reported experiments on arginine deficiency (8) in which we obtained striking evidence of atrophy of spermatogenic tissue at a time when the subjects were in nitrogen equilibrium.

Quite apart from the question of the essentiality of histidine for the adult, which obviously requires further study, is the question of the need of the growing organism for this amino acid. It may well be in the human species, as is suggested by the observations of Burroughs (3) in the rat that a peculiar need for this amino acid occurs only during the period of growth.

SUMMARY

1. Human subjects on a histidine-deficient diet remained in nitrogen equilibrium, but lost weight.

2. The histidine-deficient state was characterized by the appearance of an abnormal metabolite in urine, a substance giving a green color reaction with the Sharlit indican test.

3. Reasons are given for questioning the conclusion that histidine is a non-essential dietary constituent for man.

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PROPER ATTENTION TO THE ROLE OF EMOTIONAL AND SOCIAL FACTORS IN ILLNESS AS A NEW STEP IN PUBLIC HEALTH[1]

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Consideration of this subject must be prefaced by a brief description of an effort to give proper attention to the emotional and social factors of illness as they are encountered in the out-patient department and wards of a medical service of a general hospital. Hundreds of patients have been studied from this point of view. Most of them have been studied without selection beyond their admission to the general medical service or to certain special clinics, and without previous knowledge of their emotional and social status.

Our study of the patients was begun after their physical status had been determined by the usual clinical methods that led to a diagnosis of organic disease or functional disturbance upon which a plan of treatment was usually based. The first step in the study of emotional and social problems was an interview which gave the patient an opportunity to relate what was on his mind in relation to his illness and which led him to give an account of his social situation, his mode of living, his habits, work, recreation or anything else that seemed to throw light on the patient as a person, and to reveal evidence of what we have called "personality disorders". By this means information was obtained regarding emotional tension in the home or at work, sexual problems, moods, worries, anxieties or frustrations. Evasions or subjects about which the patient did not want to talk were also noted. In most cases several interviews were held, and many patients were visited in their homes, where members of their families were seen and questioned. Any other information such as reports from social agencies, the opinion of clergymen, teachers, out-side doctors or friends was obtained when practical in order to make our study of the patient as complete as possible.

All data on each patient was recorded by dictation, studied and later

[1] Read at the twenty-second Annual Conference of the Milbank Memorial Fund, Session on New Steps in Public Health, April 12, 1944.

reviewed and discussed with the patient, in an effort to give proper attention to emotional and social factors as a basis for a plan of treatment correlated with that which had already been prescribed. These studies indicate that about sixty-five per cent of the patients admitted to the out-patient medical service are confronted with adverse social conditions that are directly related to their illness. These adverse social conditions cause emotional disturbances in over fifty percent of the patients, and are the major precipitating cause of illness in about thirty-six per cent of the patients.

The first conviction that developed from these studies was that emotional and social problems disturb the health of a large proportion of the patients admitted to the medical service, most of whom are people of normal or average mentality, that these disturbances are often present in patients with organic disease, where they are especially likely to be overlooked, and that they frequently constitute the major cause of illness.

The second conviction was that giving proper attention to emotional and social factors of illness not only is a means of revealing the total individual and the various factors disturbing his health, but also brings to light problems of treatment that are essential to the restoration of health. It was obvious, therefore, that the study of the personal problems of the patient is a field of medical practice that deserves greater cultivation than it has had in the past, and is a component of medicine of paramount inportance in medical education.

This conviction that consideration of the patient as a total individual is necessary in good medical practice has gained much ground recently, or perhaps we should say has *re*gained much ground. This conception is beginning to find its place in university hospitals and in the curricula of medical schools, as well as being cultivated as a field of research.

If we now assume that the proper attention to the emotional and social factors of illness is of value in clinical medicine, let us give consideration to its value in the promotion of public health and preventive medicine. The study of the patient as a person as I have described it, directs the attention to the social and environmental situation of the individual whose physical status and medical diagnosis

have been determined. This widening of the view that is taken of the individual to include various factors in his surroundings and human relations that may be detrimental to his health brings to the attention of the physician factors that may be detrimental not only to the individual patient, but also to those that are intimately associated with him, or to those who live as he does in his community or even to general problems of faulty hygiene and unsanitary conditions. If the physician gives proper attention to the emotional and social factors of the illness of his patient, he soon learns to appreciate the importance of personal conflicts, of family congestion, of lack of protection from infection, of adverse conditions of work, and of nutrition, the lack of recreational and cultural opportunities and other disadvantages to public health and preventive medicine that may affect the whole community. He may be impressed too with the inadequacies in the organization of medical care, and the difficulties that prevent people from getting medical care when it can be of most value, at the first evidence of illness.

It is obvious that the physical strain of various types of work must be appreciated in directing the activities of patients with chronic, limiting disease such as circulatory damage or pulmonary tuberculosis. It is equally important to evaluate the emotional stress and strain under which patients have to live, whether they have organic disease, personality disorders or any other form of ill-health. Efforts of adjustment of the patient to his environment and of his environment to the patient are often necessary to bring the patient to the optimum state of health that his particular conditions allow.

How attention to social and emotional problems may lead from the consideration of the individual to the recognition of and interest in problems of public health in which the individual is involved may be illustrated by some personal experiences.

A colored boy of about fourteen with pulmonary tuberculosis was visited at his home with a medical student and a public health nurse, in order to study the social problems related to his illness and to instruct the family in regard to the preventive measures that should be followed. It was found that this boy had been discharged because of his illness from a training school for delinquents. The nurse said that he was the fourth boy with tuberculosis whom she had recently

visited after discharge from this institution. This experience immediately aroused my interest in this institution which had a year or so before been taken over by the State of Maryland from a private Board of Directors. This interest was a factor in my appointment by the Governor of Maryland to membership on the Board. Soon thereafter a conference at the institution was held with the Director of the State Tuberculosis Sanitoria, the Director of Communicable Diseases of the State Board of Health, the Health Officer of the County in which the institution was situated, a representative of the Maryland Tuberculosis Association and the visiting doctor. The obvious plan of giving tuberculin tests to all of the three hundred inmates and of having chest x-rays taken and evaluated by an expert of all positive reactors was carried out. This plan has been followed with all new admissions during the past four years, and all active cases have been removed to a State Tuberculosis Sanitorium. During the time this plan has been in operation, the institution has been free of active tuberculosis and all suspects have been kept under observation.

Of course, the chain of events in this instance was unusual, as a number of unrelated factors were involved between the study of the tuberculous boy and the continuing interest in the health problems of this State Training School for Colored Boys. It serves, however, to illustrate how the study of the social problems of a patient may reveal general needs and opportunities for public health activities.

Another example was a sixteen year old high school girl who complained of headaches, drowsiness and back-pain of four months duration. Thorough examinations failed to reveal any physical abnormalities, but her emotional disturbance and attitude suggested early symptoms of schizophrenia. The interview of this girl and her mother brought out a difficult school situation with unsatisfactory grades that was magnified by a stern and exacting father. The study of this girl led us into an interesting school problem which was largely solved by effecting her transfer to a vocational school. The study of this case was of value to the principals of the high school and of the vocational school to which the girl was transferred. Also, to the school nurse and to the father, who was also interviewed. It was particularly the adjustment of the father that played an important part in not only restoring the patient to a state of happy girlhood,

but relieved the emotional tension of the whole family so that the mother and the sister of the patient claimed that they were freed of disagreeable symptoms which definitely increased their sense of well-being during the year or so this family was followed.

In this case lack of satisfaction in her studies, friction in the family group relationships and consequent emotional disturbances interfering with success in carrying school work created symptoms for which the patient was brought to the hospital. It is a good example of the value of social adjustment in the treatment of illness and in the prevention of serious consequences of emotional strain treated by family education.

This case is cited, however, especially to indicate how the study of an individual may lead into an important field of public health, namely school hygiene. This experience served to stimulate an interest in the school authorities in the problems that they frequently encountered but which they tended to treat superficially and without a very clear conception of their significance. Their point of view and analysis of this case was, however, of distinct value to those who were attempting to give proper attention to emotional and social factors of illness.

Many other problems of public health and preventive medicine could be cited to which the study of the patient as a person has led. These problems may be specific for the sitution of the individual, or they may have wide significance. The important point is that medical practice should be organized so that the study of the patient as an individual leads freely and naturally into the study of the problems of preventive medicine, public health and mental hygiene as related to that individual. The proper attention to the emotional and social factors of illness makes this transition natural and uninterrupted and leads to integration and correlation of effort. The practitioners of medicine and the workers in the fields of hygiene and public health should develop a better understanding of each other's methods, material and accomplishments by working side by side.

Emotional and social disturbances may create emotional fatigue, taking its toll of mental and physical health. When this toll begins to be paid in terms of symptoms such as digestive discomforts, unusual muscular fatigue, headaches, sleeplessness, or cardiac palpitation

medical advice is sought. The person becomes conscious of "social incapacity" and develops a sense of insecurity in performing the natural activities of living, which brings him to a doctor or to a clinic. In many instances, however, people with symptoms of emotional fatigue begin by taking medicines at the advice of the drug store clerk or show lively interest in the constant radio appeals to feed on laxatives and vitamins.

This sort of harmful medication could be prevented if the relations of the medical profession to the public were such that emotional strain could be considered as a reason in itself for seeking and obtaining medical care, before illness asserted itself. If people could be educated to depend on doctors, or at least on certain types of general physicians for analysis and treatment of their emotional and social problems when they are first recognized, not only would there be fewer functional disturbances and personality disorders but also fewer cases of gastric ulcer, less asthma, perhaps fewer cases of chronic arthritis and a diminution of arterial sclerosis, hypertension and coronary disease.

If individuals were educated to the point of seeking positive health from the medical profession as well as the treatment of illness and disease, then the profession would learn to offer facilities and methods for meeting such needs. Such service is offered by some group practice in this country, and has been developed more fully by the Pioneer Health Center in what is called the Peckham Experiment (1) in England.

If the proper attention to the emotional and social factors is of the value in preventative medicine, in public health and hygiene that we believe it to be, what should be done about it?

Three suggestions may be made.

First, greater emphasis should be given to an understanding of and methods of dealing with emotional and social components of health and of illness in medical education. Students should be trained from the beginning of their clinical experience to consider every patient as a person whose emotional status has an important relation to illness and health which requires study both from the point of view of the individual and of the social setting in which that individual has lived in the past and is likely to live in the future.

Secondly, efforts should be made in the organization of medical practice by groups, hospital staffs and individual practitioners to provide for greater emphasis on positive health, of which the emotional and social factors play a larger part than is generally considered. An adjustment of the individual to the social problems he has to face and live with, and directions for living in a better state of integration with one's daily associates and family are apt to be more valuable than vacations, regimes of diet, exercise, and the regulation of individual habits that are so often the beginning and end of medical advice, based on superficial or erroneous concepts of the causes of symptoms.

The third suggestion is that the proper attention to the role of emotional and social factors of illness would serve to make the bond between the medical profession and the public stronger than it is at present. Dissatisfaction is often expressed today in regard to the mechanical methods of medical care which represents a desire of patients for a deeper understanding of their personal problems than they receive. The strengthening of the bond between the profession and the public it serves would improve the integration of the profession in our social structure and put it in a stronger position to advance public health, hygiene, and preventive medicine.

REFERENCE

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Hall, March 13, 1944

Dr. Alfred Blalock Presiding

1. Case Report: A Rare Type of Evisceration. Dr. Samuel McLanahan.

SUMMARY

The patient, a 76 year old woman suffering from chronic arthritis had been for 10 years at the Home for Incurables. She was also known to be afflicted with rectal prolapse. On her way from the commode to the bed, she collapsed on the floor and was found with many coils of apparently normal small intestine protruding from her rectum and lying between her thighs (Figure 1). The loops of intestine were covered with normal serosa and showed active peristalsis. Laparotomy disclosed a rent in the lower sigmoid colon through which had escaped the greater part of the small gut. The intestines were replaced in the peritoneal cavity, the rent brought to the surface for a colostomy, and closure effected after introducing sulfanilamide. The patient succumbed four days later from suppurative pneumonitis and peritonitis.

A survey of the literature revealed reports of five other cases of eventration of the small intestine through the rectum and anal canal. The common etiologic factor, apparently not previously observed as such, was a pre-existing prolapse of the rectum. Under this circumstance the anterior wall of the lower sigmoid or rectum becomes one of the supporting structures of the pelvic floor. Any force great enough to cause a rupture of the sigmoid or rectum can then easily produce this bizarre complication.

DISCUSSION

Dr. Alfred Blalock commented on a similar instance of this rare type of evisceration which had been observed by Dr. Duncan, following an operation for prolapse of the rectum.

2. New Drugs for the Treatment of Fungous Infections. Dr. Edmund L. Keeney.

SUMMARY

Dr. Keeney reviewed his observations on the fungistatic action of sodium proprionate in vitro and in the treatment of superficial fungous infections (Bull. Johns Hopkins Hosp. *73:* 379, 479, 1943). He then described his more recent observations on the treatment of athlete's foot with sodium proprionate and with a newer fungistatic agent, sodium undecylenate, used in the form of a 1% ointment. His

experiences at Annapolis indicated that these two fungistatic agents were apparently of equal value in the treatment of dermatophytosis of the feet.

The work described is still in the preliminary stage. The effect of varying the concentrations of these agents is being studied, as well as the effect of varying the base.

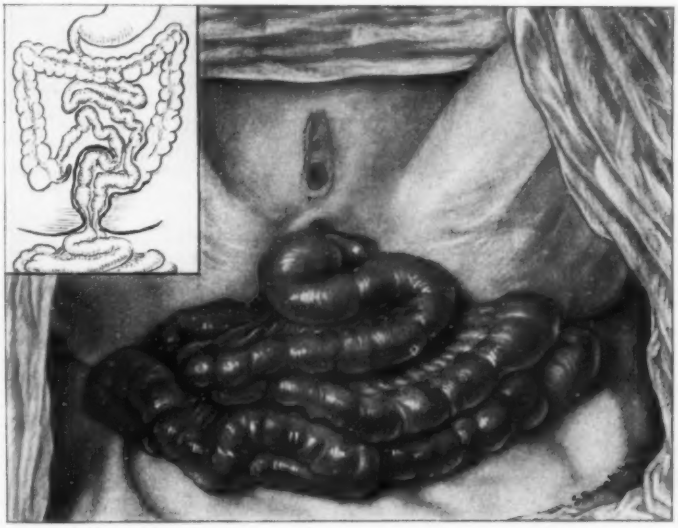

FIG. 1

DISCUSSION

Dr. Francis A. Ellis stated that no one could fail to be impressed by the therapeutic results which Dr. Keeney had presented, and by the non-irritating character of the newer agents. He said that it was apparent that these studies required an enormous amount of work by Dr. Keeney and his co-workers. However, he wished to stress the need for very careful controls in such studies. The controls should consist of cases in which the identical fungus had been recovered by culture. For example the tinea capitis cases caused by *M. Audouini* were notoriously hard to cure whereas those caused by *M. Lanosum* were relatively easy. He also wished that Dr. Keeney had mentioned the age of his tinea capitis patients, since it was well known that such cases cleared spontaneously at the age of puberty. He regretted the fact that Dr. Keeney had not run controls with the time-honored keratolytic agents such as salicylic acid. There was certainly no question about the efficacy of the newer and the older fungistatic agents in vitro, but he felt that there was a big difference between the efficacy of a drug in vitro and in vivo and that further

clinical observations were needed to establish the value of these drugs in practice. He was under the impression that Dr. Samuel Peck who had employed sodium proprionate for six years still continued to use it, but with only limited enthusiasm. The difficulties of diagnosis in these cases were often considerable and the course was highly variable; before one could be sure of the clinical efficacy of an agent, it was necessary to have an enormous number of cases which must be followed for a long time. These drugs would be a great advancement if proved of curative value in the treatment of trichophyton purpureum as this fungus disease has been considered as practically incurable.

Dr. Ellis quoted the editors of the 1943 Year Book of Dermatology & Syphilology (Page 287) who stated "Clinical evaluation of the relative value of different therapeutic agents for athlete's foot is a task beset with pitfalls and almost insurmountable difficulties. The course of the disease is erratic, remissions and exacerbations are irregular, diagnosis is difficult and often uncertain and the influences of contributory factors, from friction and foot gear to rest, climate, activities and "nervous strain," are usually impossible to exclude. Only careful clinical comparative trials, performed in huge numbers of actual cases, observed under approximately equivalent conditions can shed any light on the relative merits or demerits of different preparations for athlete's foot."

Dr. A. Murray Fisher asked about the percentage of relapses in these cases.

Dr. Alan Chesney asked Dr. Keeney to relate the story of his original interest in sodium proprionate.

Dr. Edmund L. Keeney stated that his interest in sodium proprionate began on a rainy day in Atlantic City when he was driven for shelter into the du Pont exhibit and heard a lecturer describe the virtues of sodium proprionate as a fungistatic agent in bread. Had the sun been shining that day in Atlantic City, he would not be speaking tonight.

In reply to Dr. Ellis, he would like to state that salicylic acid had been tried in controlled experiments by Dr. Hopkins whose conclusion was that it was not suitable for indiscriminate use in the armed forces. He spoke of the present attitude of Dr. Samuel Peck as decidedly enthusiastic rather than luke-warm. Replying to Dr. Fisher, he referred to the very real percentage of relapses which he felt could be attributed to lack of cooperation in carrying out treatment thoroughly and, in many instances, to reinfection.

3. Plastic Surgery for War Wounds. LT. COL. J. BARRETT BROWN.

SUMMARY

The speaker gave an illustrated talk describing some of the injuries seen in the Valley Forge General Hospital at Phoenixville, Pennsylvania and discussed their treatment.

He pointed out the differences between military and civilian plastic surgery and stressed the difficulties caused by dirt and metallic fragments in wounds. Nevertheless many of the problems were similar—notably those related to burns

and traffic accidents. Quite apart from the assistance which chemotherapy has been to the plastic surgeon, he felt that real advances had been made in surgical technique since the last war and that wounded men were receiving better treatment earlier than formerly. This results in a lower mortality but increases the problems of the plastic surgeon. He described the use of skin flaps, both simple and lined, in jaw reconstruction. He also emphasized the great value of thick free skin grafts and illustrated how the technique of this type of skin grafting has been improved.

DISCUSSION

Dr. J. Staige Davis referred to the outstanding task being performed by the guest speaker and the prodigious quantity as well as the quality of his work.

Dr. Edward M. Hanrahan pointed out that Col. Brown was probably the foremost exponent of the free thick skin graft and had had much to do with its increasing general use. This type of graft has been well known in the Johns Hopkins Hospital as it was used here by Dr. Halsted in his radical breast operations. Col. Brown had shown its great usefulness on granulating surfaces. Not everyone could cut such grafts free hand, as Col. Brown does, but a calibrated dermatome was now available which should be of great assistance to the man who was not working constantly in this field. He also stressed the speaker's contribution in showing the value of undisturbed pressure in dressing these grafts.

Lt. Col. Walter D. Wise paid a tribute to the speaker, whose work he had recently observed in person. His work was outstanding, not only from the quality and quantity of his energy, but from the extraordinary morale which he had been able to give his patients.

BOOK REVIEWS

(These reviews represent the individual opinion of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Clinical Diagnosis by Laboratory Examinations. By JOHN A. KOLMER. 1107 pp. Illus. $8.00. D. Appleton-Century Company, Inc., New York & London, 1943.

In this book, the author not only stresses the importance of laboratory examinations as an essential aid to clinical diagnosis, but also brings the two together in one well arranged and illustrated volume.

The book is conveniently divided into three parts: Part one embraces the interpretation of laboratory examinations along with an evaluation of abnormal changes in terms of Physiology and Pathology. Part two includes the laboratory findings of value in diseases of the genito-urinary and gastro-intestinal tracts, cardiovascular and respiratory systems, blood diseases, endocrine and metabolic disorders and infectious diseases where laboratory examinations are essential to diagnosis and treatment. Part three includes detailed description of the important and common laboratory methods, with adequate and up to date references to the more intricate technics of specialized laboratory procedures.

In general the book is well indexed and illustrated and includes a good selective bibliography. Each subject is treated adequately and comprehensively. It should be invaluable to the student and practitioner alike.

V. A. N.

Methods of Treatment. By L. CLENDENING and E. H. HASHINGER. 8th Ed. 1033 pp. Illus. $10.00. The C. V. Mosby and Company, St. Louis, 1943.

The fact that this volume is now in its eighth edition indicates the useful purpose it has undoubtedly served. The present edition includes much that is new in treatment, even subjects which have not yet completely passed through the wave of enthusiasm for that which is new and assumed their proper place in the armamentarium of the physician. The authors have dealt with these subjects in a conservative and restrained manner, not stifling enthusiasm for advance but at the same time adding the word of caution necessary in the proper evaluation of new methods of treatment. The arrangement is excellent; in Part II, it permits the consideration of therapeutic procedures in their relationship to specific disease, enabling one to view his task as the treatment of a sick human being. Likewise, it allows in Part I an opportunity to review various methods of treatment in sufficient detail to appreciate their indications, to understand their mode of action, and to realize what may be expected of them and their limitations as well. The volume gives due prominence to such important sections of therapeutics as dietetics, physi-

cal therapy and psychotherapy and does not permit one to forget that he is treating a sick person, which involves far more than the mere administration of drugs. The authors have approached treatment in its broad sense and it may truly be said that it is a treatise on therapy.

The work should be of particular value to the student and is to be commended to his consideration. Much information concerning various therapeutic procedures is available which would otherwise require a great deal of time and effort to obtain. He is urged to consult it with the hope that it will bring him to the realization that whereas diagnosis is indispensible and cannot be too accurate, it is for the purpose of intelligent treatment and is not a mere academic exercise. The excellent references which the authors have provided should be of particular value to the student in that they afford the opportunity to pursue the subject as far as his intellectual curiosity prompts.

This is an excellent arrangement of a subject difficult to present and may be recommended to practitioners and students alike. It is one to which they may feel they can turn with confidence.

C. W. W.

Borderlands of Psychiatry. By STANLEY COBB. 166 pp. $2.50. Harvard University Press. Cambridge, 1943.

In the opinion of this reviewer, Cobb in his Borderlands of Psychiatry, has done a notable service for psychiatry. He has set down in a short and very readable volume a superb critical analysis of a number of important fields in neuro-psychiatry. With his thorough extensive knowledge of these fields he sums up the available scientifically sound knowledge dismissing those theories which are merely verbal or too speculative. He questions openly the dogmatism of overzealous claimants. Psychoanalysists, psychobiologists, organicists and psychosomaticists —all are placed on the witness stand and convicted of too little evidence and too much claim.

Throughout the volume he stands firmly on the thesis that function and structure can never be separated without departing from the scientific method. He gives all the pertinent critically sound data from Anatomy, Physiology, Pathology, Neurology, Medicine and Sociology which throw any light upon the problems and then is always prepared to say we know nothing more at present.

He recognizes the real value of the investigators and theorists in the various fields he writes about, accepts their material when they supply scientific facts, insists that there is a valid place for any type of research from any point of view, provided the data it produces is scientific and practical. But the data has to be experimentally proved, or statistically sound. The long run test of the causal sequence is his final test. He is willing to work with the best we have but he does not regard truth and clinical workability as synonomous. He gives due place to clinical facts and experience but clinical data must be critically examined in light of experimental data where the evidence is clearer, controllable and more clean cut.

His first chapter on Body and Mind gives a series of cases to demonstrate that a

contrast between Body and Mind falls to earth because from these cases it is clear that there can be no sensible separation between what is functional and organic. He proposes that in our present state of knowledge that we accept multiplicity of causes,—genogenetic (hereditary) histogenic (due to visible lesions of tissue), chemogenic (due to ultra microscopical changes in tissue), and psychogenic (due to maladjustments in interpersonal relations).

His second chapter deals with the parallel evolution of speech, vision, and intellect, and leads into his second chapter on speech and language defects. He makes a clear statement of need for understanding the successive levels of functional integration in the central nervous system. His clear discussion of aphasic disorders is an excellent example of his ability to see a very complicated field in a simple, illuminating manner.

Then follows a fourth chapter on the function of the frontal lobes with a critical evaluation of frontal lobotomy. Even in spite of his very conservative attitude toward the operation, he is open-minded and fair in his evaluation of the operation.

His discussion of the anatomical basis of the emotions in chapter five presents a critical survey of anatomical and physiological data. My only reservation about the presentation is that too little stress is laid upon the whole field of emotional states. It is true that rage, fear, and mating emotions have been the ones most studied experimentally, but why leave out of emphasis, much of the emotional material of psychiatry—the elative, excitement emotions?

The chapters on consciousness with its discussion on sleep and the one on fits gives the newest data on encephalographic studies. The "fit" is presented in its proper setting of a multiplicity of causes—predisposition, brain instability, and psychologic and situational stresses.

Then follows a longer chapter on the psychoneuroses (Chapter VIII). This discussion is practical clinically, and admits that at present out information about causality is meagre He prefers description and clinical experience to dogmatic theorizing about the few facts available.

A final chapter on psychosomatics is a very guarded statement about this "new" field of medicine. Cobb insists that the evidence be critically surveyed and quotes Wolff to sum his point of view.

"If our generation is to make any contribution to this subject, it would seem to me that it is in the direction of stating how much or how little or in what direction these bodily changes occur. If we repeat verbalizations of this relationship, we add but little. If we actually devise means to study the amount of these changes, we may be able to detect new relations not now known to exist. Our job now, it seems is to be creative in methods of inducing various emotional states and using at the same time the tools that we have been given to measure accompanying bodily changes. If we do this, we will be able to say to what extent fear is related to ulcers of the stomach, to what extent Raynaud's syndrome is associated with anxiety, to what extent Graves' disease is related to stress."

I insist that Cobb's book is one that every student and physician including the high and low in medicine should at least read and most should own for repeated

reading. It has a constructive point of view and is a superb critical summary of the Borderlands of Psychiatry.

L. B. H.

Handbook of The Lying-In Hospital. Woman's Clinic of the New York Hospital. 158 pp. $2.00. Woman's Clinic of the New York Hospital, New York, 1942.

This handbook describes in detail the routine procedures and techniques of the Woman's Clinic of the New York Hospital. As a manual for the instruction and guidance of new members of the house staff of that institution it should be most valuable, while as a presentation of the procedures used in a large and well conducted woman's clinic it will be informative to all obstetricians and gynecologists.

N. J. E.

Workmen's Compensation and the Physician. By HENRY H. JORDON. 180 pp. $3.00. Oxford University Press, New York (etc.) 1941.

In spite of the fact that this author has prepared this small text for the use of compensation insurance carriers and practitioners who ordinarily do not see patients suffering with compensible injuries, the industrial surgeon will find it of great interest. It is not a text describing traumatic surgery or treatment of fractures, but rather a reference text for general practitioners and insurance carriers to assist them in the handling of patients suffering from compensible injuries.

The subject matter is limited to general therapeutic and diagnostic procedures, and includes a discussion of such questions as the aggravation of pre-existing disease, the causal relation between injury and disability, expert opinion and disability evaluation. The author emphasizes the importance of complete records and examination to assist in arriving at diagnosis. In discussing treatment he goes into considerable detail concerning orthopedic appliances and physical therapy. In addition, there is a discussion of traumatic neuroses, by Dr. Paul H. Hoch, and a two page list of references.

The book will be of extreme value in the states where the general practitioners of medicine are allowed by law to participate in the management of workmen's compensation cases.

E. L. C.

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